Texas Medicaid/CHIP Vendor Drug Program
Drug Utilization Criteria For Outpatient Use Guidelines
Angiotensin II Receptor Blockers

About
Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Publication History
Revised December 2016; October 2014; December 2012; March 2011; April 2008; July 2003; July 2002; September 2001; September 2000; July 1999; June 1998; July 1997; December 1996. Developed August 1996.

---

1. Dosage [*]
Adults
Angiotensin II receptor blockers (ARBs) as monotherapy are FDA-approved for use in hypertension (all available ARBs), diabetic nephropathy (irbesartan, losartan), heart failure (candesartan, valsartan), stroke prophylaxis (losartan), cardiovascular risk reduction in patients unable to take angiotensin-converting enzyme (ACE) inhibitors (telmisartan), and post-myocardial infarction (valsartan). ARB combination therapy is FDA-approved for use in hypertension [all available ARB combinations, **including the newer combination, nebivolol/valsartan (Byvalson®)**] and stroke risk reduction in hypertensive patients as well as patients with left ventricular hypertrophy (Hyzaar®). **Sacubitril/valsartan (Entresto®) combination therapy is FDA-approved to reduce the risk of cardiovascular death and hospitalization in chronic heart failure with reduced ejection fraction.** The maximum recommended daily doses assigned to ARBs as monotherapy and combination therapy for adult patients are summarized in Tables 1 and 2. Patient profiles containing ARB dosage regimens exceeding these recommendations will be reviewed.

Table 1: Maximum Daily Adult Dosages for Angiotensin II Receptor Blockers - Monotherapy

Medication	Dosage Form/Strength	Recommended Maximum Dosage
azilsartan (Edarbi™)	**40 mg, 80 mg tablets**	80 mg/day
candesartan (Atacand®, generics)	**4 mg, 8 mg, 16 mg, 32 mg tablets**	32 mg/day
eprosartan (**generics**)	**600 mg tablets**	800 mg/day
irbesartan (Avapro®, generics)	**75 mg, 150 mg, 300 mg tablets**	300 mg/day
losartan (Cozaar®, generics)	**25 mg, 50 mg, 100 mg tablets**	100 mg/day
olmesartan (Benicar®, **generics**)	**5 mg, 20 mg, 40 mg tablets**	40 mg/day
telmisartan (Micardis®, generics)	**20 mg, 40 mg, 80 mg tablets**	80 mg/day
valsartan (Diovan®, generics)	**40 mg, 80 mg, 160 mg, 320 mg tablets**	320 mg/day

Table 2: Maximum Daily Adult Dosages for Angiotensin II Receptor Blockers - Combination Therapy		
Medication	**Dosage Form/Strength**	**Recommended Maximum Dosage**
amlodipine/olmesartan (Azor®, **generics**)	**5 mg/20 mg, 10 mg/20 mg, 5 mg/40 mg, 10 mg/40 mg tablets**	10 mg/40 mg/day
amlodipine/valsartan (Exforge®, **generics**)	**5 mg/160 mg, 5 mg/320 mg, 10 mg/160 mg, 10 mg/320 mg tablets**	10 mg/320 mg/day
amlodipine/valsartan/ hydrochlorothiazide (Exforge® HCT, **generics**)	**5 mg/160 mg/12.5 mg, 10 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/25 mg, 10 mg/320 mg/25 mg tablets**	10 mg/320 mg/25 mg/day
azilsartan/chlorthalidone (Edarbyclor®)	**40 mg/12.5 mg, 40 mg/25 mg tablets**	40 mg/25 mg/day
candesartan/hydrochlorothiazide (Atacand HCT®, generic)	**16 mg/12.5 mg, 32 mg/12.5 mg, 32 mg/25 mg tablets**	32 mg/25 mg/day
irbesartan/hydrochlorothiazide (Avalide®, generic)	**150 mg/12.5 mg, 300 mg/12.5 mg tablets**	300 mg/25 mg/day
losartan/hydrochlorothiazide (Hyzaar®, generic)	**50 mg/12.5 mg, 100 mg/12.5 mg, 100 mg/25 mg tablets**	100 mg/25 mg/day
nebivolol/valsartan (Byvalson®)	**5 mg/80 mg tablets**	**5 mg/80 mg/day**
olmesartan/amlodipine/ hydrochlorothiazide (Tribenzor®, **generics**)	**20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/5 mg/25 mg, 40 mg/10 mg/12.5 mg, 40 mg/10 mg/25 mg tablets**	40 mg/10 mg/25 mg/day
olmesartan/hydrochlorothiazide (Benicar HCT®, **generics**)	**20 mg/12.5 mg, 40 mg/12.5 mg, 40 mg/25 mg tablets**	40 mg/25 mg/day
sacubitril/valsartan (Entresto®)	**24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg tablets**	**194 mg/206 mg/day**
telmisartan/amlodipine (Twynsta®, generics)	**40 mg/5 mg, 40 mg/10 mg, 80 mg/5mg, 80 mg/10 mg tablets**	80 mg/10 mg/day
telmisartan/hydrochlorothiazide (Micardis HCT®, generics)	**40 mg/12.5 mg, 80 mg/12.5 mg, 80 mg/25 mg tablets**	160 mg/25 mg/day
valsartan/hydrochlorothiazide (Diovan HCT®, generic)	**80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, 320 mg/ 25 mg tablets**	320 mg/25 mg/day

Pediatrics
Candesartan has recently been FDA-approved to manage hypertension in children 1 to < 17 years of age. Losartan, olmesartan, and valsartan are FDA-approved to manage hypertension in pediatric patients 6 years of age and older. Irbesartan is not FDA-approved for use in pediatric patients and has not demonstrated sustained efficacy in managing elevated blood pressure in patients 6 years of age and older. Recommended dosages are summarized in Table 3. Dosages exceeding these recommendations will be reviewed.

Table 3: Maximum Recommended Dosages for Select Angiotensin II Receptor Blockers in Pediatric Patients*	
DRUG	MAXIMUM RECOMMENDED DOSE
candesartan	*1 to < 6 years of age:* 0.4 mg/kg/day *6 to < 17 years of age:* < 50 kg: 16 mg/day > 50 kg: 32 mg/day
losartan	*6 years and older:* 1.4 mg/kg/day to a maximum of 100 mg/day
olmesartan	*6 to 16 years of age:* < 35 kg: 20 mg/day ≥ 35 kg: 40 mg/day
valsartan	*6 to 16 years of age:* 2.7 mg/kg/day to a maximum of 160 mg/day

**irbesartan (off-label) for patients 6 to 16 years of age in doses up to 4.5 mg/kg/day did not effectively lower blood pressure*

The safety and efficacy of azilsartan, eprosartan, and telmisartan in pediatric patients have not been established. The safety and efficacy of ARBs in combination with hydrochlorothiazide, aliskiren, or amlodipine in pediatric patients have not been established. **Nebivolol/valsartan and sacubitril/valsartan combination therapy is not recommended for use in pediatric patients as safety and efficacy have not been established in this patient population.**

2. **Duration of Therapy**
There is no basis for limiting therapy duration for ARBs as reduction of cardiovascular mortality post-myocardial infarction, stroke risk reduction, managing hypertension, treating diabetic nephropathy, and managing heart failure requires chronic treatment.

3.* **Duplicative Therapy**
Administration of two or more ARBs concurrently is not justified. Additional therapeutic benefit is not appreciated when multiple ARBs are utilized concomitantly. Patient profiles containing regimens comprised of two or more ARBs administered concurrently will be reviewed.

Recent studies have documented concurrent administration of ARBs and ACE inhibitors may result in an increased incidence of adverse effects (e.g., hypotension, hyperkalemia, syncope, renal failure) in patients with heart failure due to myocardial infarction or left ventricular dysfunction, as well as other patients at high risk for vascular events (e.g., diabetic patients) without added benefit. Additional studies have not documented significant benefit with ACE inhibitor-ARB combination therapy in managing hypertension or diabetic nephropathy. The American College of Cardiology/American Heart Association guidelines state that ARB-ACE inhibitor combination therapy may be considered in heart failure patients, not recently post myocardial infarction, who have not responded to target doses of an ACE inhibitor and beta blocker. Adjunctive administration of ARBs and ACE inhibitors should be considered cautiously, if at all, in these patient populations.

4.* **Drug-Drug Interactions**
Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for ARBs are summarized in Table 4. Only those drug-drug interactions classified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed:

Table 4: ARB Drug-Drug Interactions				
TARGET DRUG	INTERACTING DRUG	INTERACTION	RECOMMENDATION	CLINICAL SIGNIFICANCE LEVEL*
ARBs, **nebivolol/ valsartan, sacubitril/valsartan**	aliskiren	increased risk for renal impairment, hyperkalemia, and hypotension with adjunctive administration most likely due to additive effects; documented in ALTITUDE trial (type 2 diabetics with renal impairment had increased stroke, renal complications, hypotension when given ARBs and aliskiren concurrently)	combined administration in diabetics contraindicated by manufacturer; **avoid combination in patients with CrCl < 60 ml/min;** use cautiously together in other patients and closely monitor renal function, serum potassium levels	contraindicated (DrugReax) 2-major (CP)
ARBs, **nebivolol/ valsartan, sacubitril/valsartan**	lithium	potential for enhanced lithium pharmacologic/adverse effects with combined administration; speculated that ARBs augment lithium reabsorption by decreasing lithium renal excretion	monitor patients for increased signs/symptoms of lithium toxicity and adjust lithium doses as necessary; may select alternate cardiovascular therapy that does not interact with lithium	major (DrugReax) 3-moderate (CP)
ARBs**, nabivolol/ valsartan, sacubitril/valsartan**	nonsteroidal anti-inflammatory drugs	combined administration may increase risk for renal function deterioration and alter response to antihypertensives, especially in volume-depleted, elderly, or renally compromised patients, due to vasodilatory prostaglandin inhibition	monitor renal function, antihypertensive efficacy when combined administration required	moderate (DrugReax) 3-moderate (CP)

Table 4: ARB Drug-Drug Interactions (continued)				
Target Drug	**Interacting Drug**	**Interaction**	**Recommendation**	**Clinical Significance Level*+**
ARBs, **nabivolol/ valsartan, sacubitril/valsartan**	potassium-sparing diuretics (e.g., amiloride, spironolactone, triamterene), potassium supplements	combined therapy may increase risk for hyperkalemia as ARBs reduce circulating aldosterone concentrations, resulting in potassium retention; elderly as well as patients with impaired renal function, diabetes, or high potassium diets may be at greater risk	measure serum potassium concentrations, monitor for signs and symptoms of hyperkalemia when administered concurrently, especially in patients with predisposing factors	moderate (DrugReax) 2-major (CP)
nebivolol/valsartan	**CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine)**	**adjunctive administration may result in enhanced nebivolol pharmacologic effects (e.g., reduced heart rate, hypotension) due to increased nabivolol serum levels as nebivolol is metabolized by CYP2D6**	**combined use should be avoided; if concurrent administration necessary, monitor patients for unwanted pharmacologic/adverse effects; adjust dosages as needed**	**major (DrugReax) 2-major (CP)**

Table 4: ARB Drug-Drug Interactions (continued)				
Target Drug	**Interacting Drug**	**Interaction**	**Recommendation**	**Clinical Significance Level*+**
nebivolol/valsartan	**hypotensive agents**	**Concurrent administration may result in large reductions in sympathetic activity due to added beta-blocking activity; patients may have increased orthostasis and bradycardia**	**avoid nebivolol use with other beta blockers; withdraw nebivolol slowly over several days in patients prescribed clonidine concurrently**	**2-major, 3-moderate (CP)**
nebivolol/valsartan	**digitalis glycosides**	**co-administration may increase bradycardia risk as both nebivolol and digitalis glycosides reduce atrioventricular conduction and decrease heart rate**	**administer nebivolol with digitalis glycosides cautiously and monitor heart rate**	**moderate (DrugReax) 3-moderate (CP)**
nebivolol/valsartan	**calcium channel blockers**	**combined use of beta blockers like nebivolol with calcium channel blockers can be useful in some circumstances; however, combined administration may result in additive negative inotropic and/or chronotropic effects**	**If combined therapy needed, monitor heart rate and cardiac conduction; adjust doses as necessary**	**moderate (DrugReax) 3-moderate (CP)**

**Clinical Pharmacology*

REFERENCES

1. Azilsartan tablets (Edarbi™) package insert. **Arbor Pharmaceuticals, Inc./Takeda**, **May 2014**.
2. Candesartan tablets (Atacand®) package insert. AstraZeneca, **July 2016**.
3. Eprosartan tablets package insert. **Mylan Pharmaceuticals, Inc., December 2014**.
4. Irbesartan tablets (Avapro®) package insert. Sanofi-Aventis, **February 2016**.
5. Losartan/hydrochlorothiazide tablets (Hyzaar®) package insert. Merck & Co., Inc., **December 2015**.
6. Losartan tablets (Cozaar®) package insert. Merck & Co., **December 2015**.
7. Olmesartan tablets (Benicar®) package insert. Daiichi Sankyo, Inc., **May 2016**.
8. Olmesartan/amlodipine/hydrochlorothiazide tablets (Tribenzor®) package insert. Daiichi Sankyo, Inc., **November 2016**.
9. Telmisartan tablets (Micardis®) package insert. Boehringer Ingelheim Pharmaceuticals, Inc., **December 2014**.
10. Telmisartan/hydrochlorothiazide tablets (Micardis® HCT) package insert. Boehringer Ingelheim Pharmaceuticals, Inc., **January 2016**.
11. Telmisartan/amlodipine tablets (Twynsta®) package insert. Boehringer Ingelheim Pharmaceuticals, Inc., **January 2016**.
12. Valsartan tablets (Diovan®) package insert. Novartis, **September 2016**.
13. Valsartan/hydrochlorothiazide tablets (Diovan HCT®) package insert. Novartis, **July 2015.**
14. Amlodipine/valsartan tablets (Exforge®) package insert. Novartis, **August 2015**.
15. Amlodipine/valsartan/hydrochlorothiazide tablets (Exforge® HCT) package insert. Novartis, **July 2015.**
16. Azilsartan/chlorthalidone (Edarbyclor®) package insert. **Arbor Pharmaceuticals, Inc./Takeda, April 2015**.
17. **Nebivolol/valsartan (Byvalson®) package insert. Allergan USA, Inc., June 2016.**
18. **Sacubitril/valsartan (Entresto®) package insert. Novartis, August 2015.**
19. DRUGDEX® System (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.thomsonhc.com.libproxy.uthscsa.edu. **Accessed December 2nd, 2016.**
20. Redbook® Online (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.thomsonhc.com.libproxy.uthscsa.edu. **Accessed December 2nd, 2016.**
21. **Facts and Comparisons eAnswers [database online]. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.;2016. Available at: http://eanswers.factsandcomparisons.com.ezproxy.lib.utexas.edu/. Accessed December 2nd, 2016.**
22. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc; **2016.** Available at: http://www.clinicalpharmacology.com. **Accessed December 2nd, 2016.**
23. Litwin M, Grenda R, Sladowska J, Antoniewicz J. Add-on therapy with angiotensin II receptor 1 blocker in children with chronic kidney disease already treated with angiotensin-converting enzyme inhibitors. Pediatr Nephrol. 2006;21:1716-22.
24. Majani G, Giardini A, Opasich C, et al. Effect of valsartan on quality of life when added to usual therapy for heart failure: results from the Valsartan Heart Failure Trial. J Cardiac Fail. 2005;11:253-9.
25. Fujisawa T, Ikegami H, Ono M, et al. Combination of half doses of angiotensin type 1 receptor antagonist and angiotensin-converting enzyme inhibitor in diabetic nephropathy. Am J Hypertens. 2005;18:13-7.
26. Cocco G, Kohn S, Jerie P. Effects of combined treatment with enalapril and losartan on myocardial function in heart failure. Heart. 2002;88:185-6.
27. Bohm M. Angiotensin receptor blockers versus angiotensin-converting enzyme inhibitors: where do we stand now? Am J Cardiol. 2007;100(suppl):38J-44J.

28. Matchar DB, McCrory DC, Orlando LA, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. Ann Intern Med. 2008;148:16-29.
29. McCall KL, Craddock D, Edwards K. Effect of angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers on the rate of new-onset diabetes mellitus: a review and pooled analysis. Pharmacotherapy. 2006;26:1297-306.
30. Finnegan PM, Gleason BL. Combination ACE inhibitors and angiotensin II receptor blockers for hypertension. Ann Pharmacother. 2003;37:886-9.
31. The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358:1547-59.
32. Phillips CO, Kashani A, Ko DK, et al. Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction. A quantitative review of data from randomized clinical trials. Arch Intern Med. 2007;167:1930-6.
33. Baker WL, Coleman CI, Kluger J, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers for ischemic heart disease. Ann Intern Med. 2009;151(12):861-71.
34. Catanzaro DF, Frishman WH. Angiotensin receptor blockers for management of hypertension. South Med J. 2010;103(7):669-73.
35. Holdiness A, Monahan K, Minor D, de Shazo RD. Renin angiotensin aldosterone system blockade: little to no rationale for ACE inhibitor and ARB combinations. Am J Med. 2011;124(1):15-9.
36. The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358(15):1547-59.
37. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240-e327.
38. **Yancy CW, Jessup M, Bozkurt B et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016;68:1476–88.**
39. **James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-20.**
40. U.S. Food and Drug Administration. FDA Drug Safety Communication: new warning and contraindication for blood pressure medicines containing aliskiren (Tekturna). (April 20, 2012) Available at: http://www.fda.gov/Drugs/DrugSafety/ucm300889.htm . **Accessed December 2nd, 2016.**
41. DRUG-REAX® System (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com.libproxy.uthscsa.edu/. **Accessed December 2nd, 2016.**

Prepared by

- Drug Information Service, the University of Texas Health Science Center at San Antonio.
- The College of Pharmacy, the University of Texas at Austin.